

HIV Infections and Highly Active Anti-Retroviral Therapy

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Abstract

HIV (human immunodeficiency virus) is a lentivirus that causes acquired immunodeficiency syndrome. It is a condition in humans in which progressive failure of the immune system occurs. Antiretroviral therapy is used for treatment and prevention of HIV infection. Widespread use of antiretroviral agents and increasing occurrence of HIV strains resistant to these drugs has given rise to a number of important issues. There is no drug to cure HIV. To prevent drug resistance combinations of antiretroviral drugs are given. Antiretroviral therapy has been shown to prolong survival in persons with acquired immunodeficiency syndrome (AIDS) and those with intermediate-stage human immunodeficiency virus (HIV) infection.

Keywords: HIV, AIDS, HAART, Retrovirus

INTRODUCTION

World Health Organization stated in its recent report that globally 35 million people are living with HIV and about 1.5 million people died of HIV-related illnesses worldwide. An estimated 0.8% of adults aged between 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Expanded access to antiretroviral (ARV) therapy and a declining incidence of HIV infection have led to a steep fall globally in the number of adults and children dying from HIV-related causes [1].

Epidemiology and prevalence

It has been believed that HIV epidemic arose subsequent to zoonotic infections with simian immunodeficiency viruses from African primates; bushmeat hunters were probably the first group to be infected with HIV. There are two types of HIV have been identified *i.e.*, HIV-1 and HIV-2. HIV-1 was transmitted from apes and HIV-2 from sooty mangabey monkeys [2] Four groups of HIV-1 exist and represent three separate transmission events from chimpanzees (M, N, and O), and one from gorillas (P). Groups N, O, and P are restricted to West Africa. Group M, which is the cause of the global HIV pandemic, started about 100 years ago and consists of nine subtypes: A–D, F–H, J, and K. Subtype C predominates in Africa and India, and accounted for 48% of cases of HIV-1 in 2007 worldwide. Subtype B predominates in Western Europe, the Americas, and Australia.[3]

According to United Nations Programme on HIV and AIDS (UNAIDS) HIV prevalence is increasing worldwide because people on ARV therapy are living longer, although new infections decreased from 3.3 million in 2002, to 2.3 million in 2012. Moreover, global AIDS-related deaths peaked at 2.3 million in 2005, and decreased to 1.6 million by 2012. An estimated 9.7 million people in low-income

and middle-income countries had started antiretroviral therapy by 2012 [1] Hence, in this article, we systematically review the scientific literature on HAART therapy to document its advantages and disadvantages and highlight promising strategies to address AIDS.

Human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS)

Human immunodeficiency virus is lentivirus belongs to family of retroviridae and causes AIDS and is the last stage in the wide spectrum of clinical features in HIV infections and representing the irreversible breakdown of immune defense mechanisms, leaving the patient prey to progressive opportunistic infections and malignancies [4]. Primary infection with HIV is accompanied by an acute flu-like illness followed by a relatively long period of asymptomatic infection, the delayed appearance of lymphadenopathy and a progressive decline in immune responsiveness. Eventually, significant reduction in T4 cell number occurs along with susceptibility to a variety of opportunistic infections [5] It has been concretely proved that the hallmark of HIV infection is the progressive depletion of CD4 T cells because of reduced production and increased destruction. CD4 T cells are eliminated by direct infection [6] Thus, the low CD4 counts indicates a weakened immune system and a higher chance of acquiring opportunistic infections.

Monotherapy for HIV infections

Zidovudine (3' azido-3'-deoxythymidine, ZDV, AZT, Retrovir), first ARV drug synthesized in 1987 for use as a chemotherapeutic agent, is approved by the Food and Drug Administration (FDA) for therapy of human immunodeficiency virus (HIV) infection [7] Over the past 3 decades drugs belonging to 3 classes have been introduced for the treatment of ARV therapy *i.e.*, reverse transcriptase

inhibitors (RTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PIs). Owing to rapid development of resistance to monotherapy with any ARV drug and inevitable therapeutic failure and hence, HIV infection currently treated with a combination of 3 or more ARV drugs called 'highly active antiretroviral therapy'.

HAART Therapy

The introduction of highly active antiretroviral therapy (HAART) has had a dramatic impact on the morbidity and mortality of individuals living with HIV [8]. Combination ARV therapy regimens were able to suppress viral replication and were developed in the late 1990s and transformed HIV from a progressive illness with a fatal outcome into a chronic manageable disease. In 1996, HAART combination regimens have significantly abridged the mortality rate of HIV infected patients. In fact, over time moving from the pre-HAART era in which no HAART regimen were available, to the early and then late HAART eras in which not only have more antiretroviral therapies been developed but also new combinations have been tested in HIV infected individuals, clinical outcomes have improved dramatically [4]. In addition to contributing to declines in the incidence of several opportunistic infections, HAART is affecting the incidences of several AIDS-defining malignancies [8].

Standard regimen of HAART Therapy

The goal of HAART is to reduce viral replication to below the limit of detection of standard clinical assays. A relevant unresolved issue is the CD4 cell count at which HAART should be started in patients with asymptomatic infection [9]. The recommended standard of care in treatment-naïve patients include a triple combination therapy of two nucleoside reverse transcriptase (NRTIs) and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz. [10]. Several effective NRTIs-sparing regimens can be used if intolerance or resistance to NRTIs develops. Clinically, the above said HAART regimen is effectively suppress HIV replication and plasma HIV RNA level are greatly reduced and prolongs HIV infected patient's survival [11].

Hallmark of HAART therapy

These recommended HAART therapy regimens are less toxic, more effective, have a lower pill burden, and are used less frequently than the initial protease inhibitor-based regimens [12]. The potential benefit of HAART therapy includes preservation of the immune system, a decrease in the risk of HIV transmission, and earlier suppression of viral replication. The probability of classical infections and tumors attributed to HIV were dramatically reduced and life expectancy correspondingly increased [13]. Studies have also reported that HAART therapy leads to decrease in mortality by hepatic disease and to a decrease in fibrosis progression rates. This indicates the fact that the absence of HAART treatment in coinfecting patients lead to hepatic disease progression and death [14,15,16].

In addition to anti-retroviral activity, HAART therapy have also implicated in the treatment of oral candidiasis in HIV infective patients. HIV-positive patients receiving HAART suffer significantly fewer oral infections with the opportunistic fungal pathogen *Candida albicans* than non-HAART-treated patients. The advent of HAART has changed the epidemiology of candidiasis, with many studies have reported decrease in prevalence [17]. Although, overall death remained low at the beginning of last decade, the proportion of deaths attributable to non-AIDS diseases increased and prominently included hepatic, cardiovascular and pulmonary diseases, as well as non-AIDS malignancies. Longer time spent receiving HAART and higher CD4 cell counts at HAART initiation were associated with death from non-AIDS causes. CD4 cell count at time of death increased over time [18].

Spectrum of side effects in HAART therapy

There are number of problems associated with HAART, including the development of drug resistance, the difficulties of maintaining long-term adherence, and drug-related toxicities [19] all of which in turn leads to virological failure, which in turn leads to immunological failure and clinical progression [20]. Even though the life expectancy of HIV-infected patients under HAART has been extended, the various HAART-induced side effects significantly affect quality of life. Hence, we highlight some of the important side effects which are associated with HAART therapy.

Pregnancy

During pregnancy there are changes in the coagulation and fibrinolytic system and knowledge of these physiological changes characterized by hemodilution, changes in the concentration of one or more plasma protein fractions, and reduced fibrinolytic activity is necessary to manage two of the more serious problems in pregnancy; namely hemorrhage and thromboembolic diseases [21]. Increased levels of plasma protein and reduced fibrinolytic activity have been reported in pregnancy [22]. While prolonged euglobulin lysis time (ELT) and increased levels of fibrinogen have also been observed in pregnancy [23]. HAART therapy is said to cause changes in fibrinolytic activity, which may predispose pregnant women to hyperfibrinogenemia and anemia [11].

Sexual behavior

Studies were also reported the effect of HAART therapy on Sexual risk behavior in HIV infected patients. HIV-positive patients receiving HAART did not exhibit increased sexual risk behavior, even when therapy achieved an undetectable viral load. However he also stated that peoples beliefs about HAART and viral load may promote unprotected sex and may be amenable to change through prevention messages [24].

Hepatotoxicity

Elevation of hepatotoxicity marker enzymes has been reported to be a potential side effect of most antiviral agents used for the treatment of HIV-1 infection [25]. This

may be due to the hepatotoxic potential of HAART therapy. HIV-1 infected patients co-infected with HBV or HBC were at considerably higher risk of developing liver enzyme elevation during the HAART therapy when compared with patients without co-infection, but is usually not necessary to modify antiretroviral therapy [26] It has been reported that HIV/HCV co infection may increase the risk of developing hepatic disease after ARV therapy is started, and chronic hepatitis C acts as an independent risk factor for the progressions of hepatic disease and hepatotoxicity in co infected patients during HAART [27,18]

AIDS dementia complex (ADC)

Dorea et al. (1999)[29] reported that proportional increase in ADC compared with other AIDS-defining illnesses (ADIs) and a marked increase in the median CD4 cell count at ADC diagnosis have occurred since the introduction of HAART therapy. These changes suggested that HAART has a lesser impact on ADC than on other ADIs, with the poor penetration of many antiretroviral agents. However, further studies are warranted on these lines.

CONCLUSION

HIV cannot be cured but there are methods to reduce severity and prolongs life expectancy. New agents with entirely different mechanism of action as well as improved generations of current drugs that display more favorable pharmacokinetics, lower toxicity profiles and have activity against strains resistant to currently available agents can be developed. New technologies such as drug monitoring, genetic testing and improved resistance testing may also expedite achievement of therapeutic goals. The expansion of HIV treatment to new populations presents unique challenges, and the use of antiretroviral for preventative treatment, while it may save millions of lives, may also risk making resistance to the most commonly used agents worldwide.

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